Stem Cell Therapy in AKI

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Stem cells

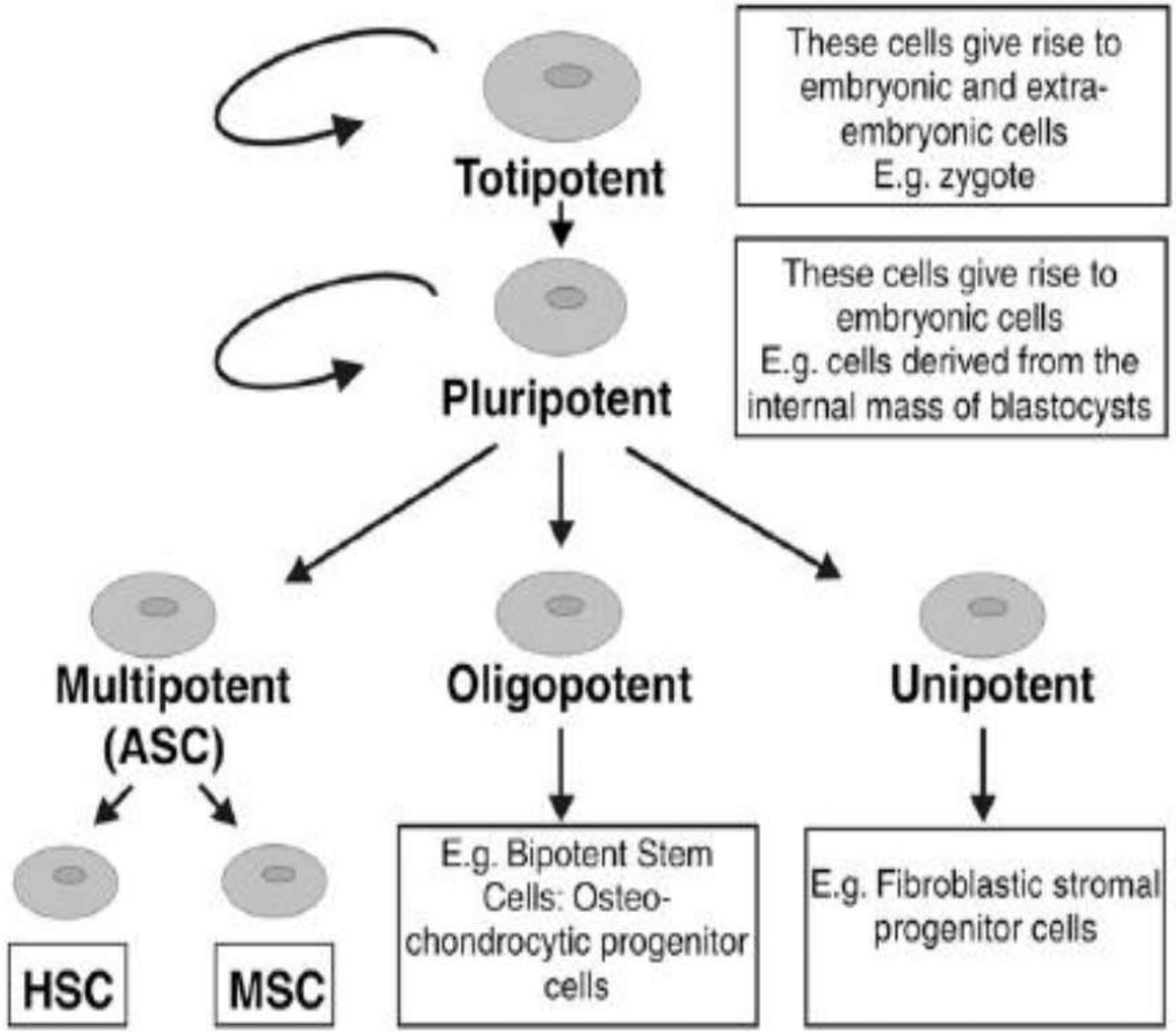
- Biological cells found in almost all multicellular organisms
- Can divide and differentiate into diverse cell types during early life and growth (Unspecialized)
- Can self-renew to produce more stem cells (Self renewal)
- Able to be induced to develop into specific cell types *in vivo* under certain activation mechanisms and signaling pathways (Differentiation)
- In many tissues they serve as a sort of internal repair system, dividing without limit to replenish other cells

Ren et al., Stem cells translational medicine, 2012;(1): 51-58

Classification

I. According to potency

Fernandez et al., 2013
Differentiation;85(1-2):1-10



II. According to origin

- Embyonic stem cells (Totipotent – Pluripotent)
- Fetal stem cells (Pluripotent)
- Cord blood stem cells (Multipotent)
- Adult stem cells (Multipotent)
- Induced pluripotent stem cells

Adult stem cells

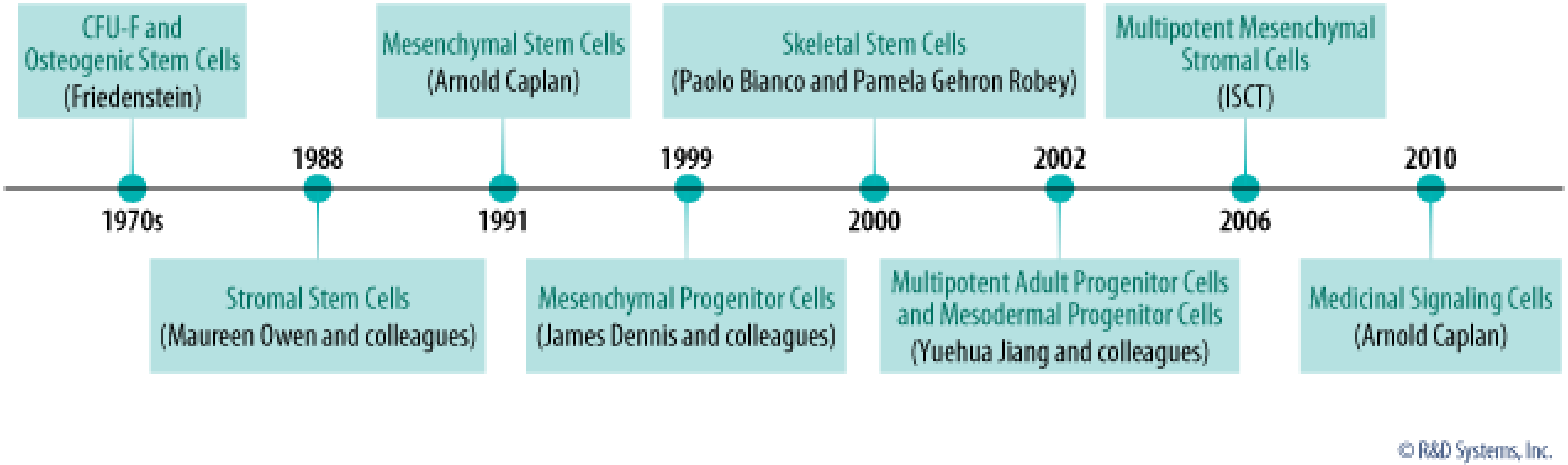
1. BM derived stem cells:

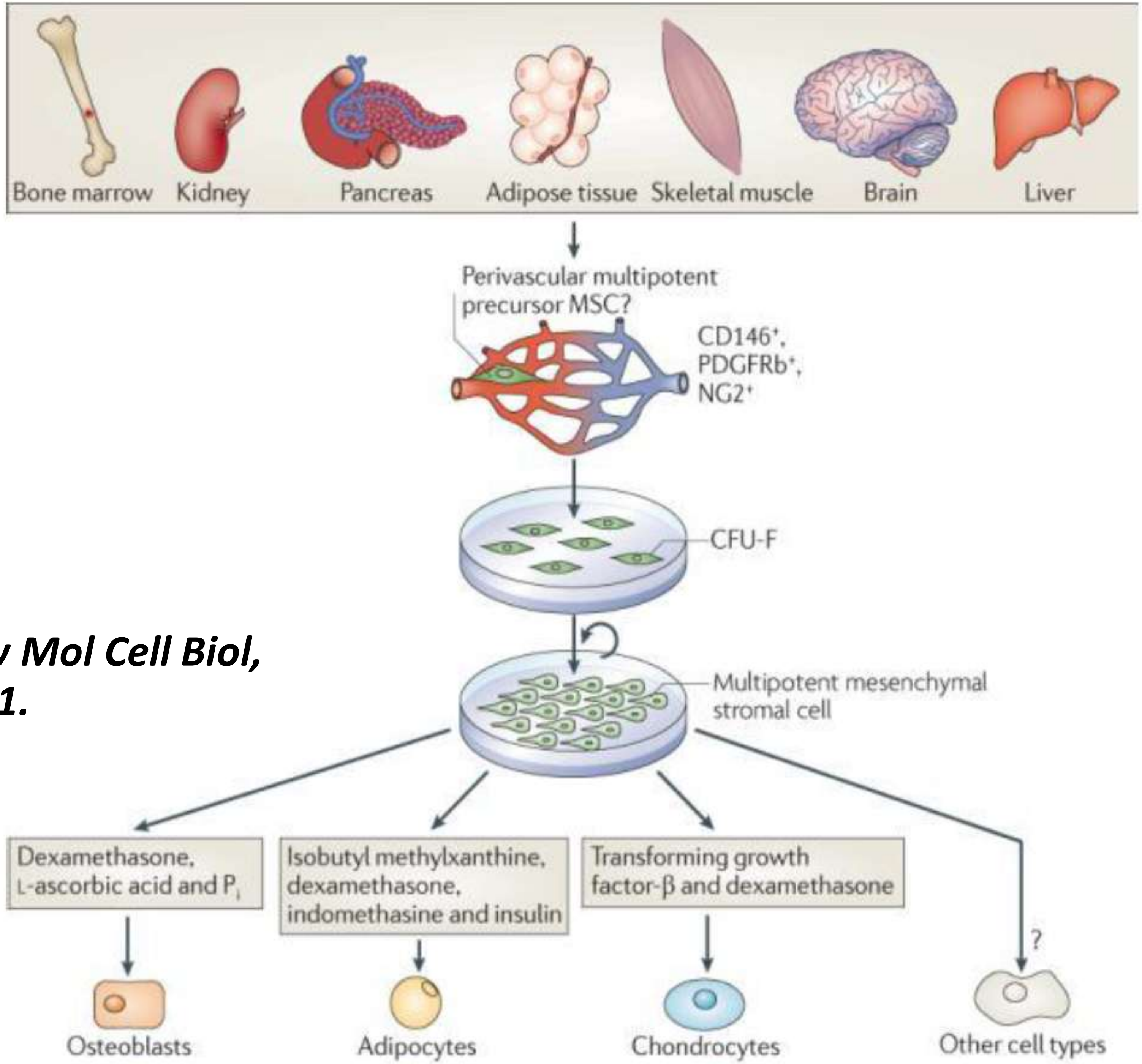
- Hematopoietic stem cells (HSCs)
- Mesenchymal stem cells (MSCs)

2. Cardiac stem cells

3. Neuronal stem cells

Mesenchymal stem cells

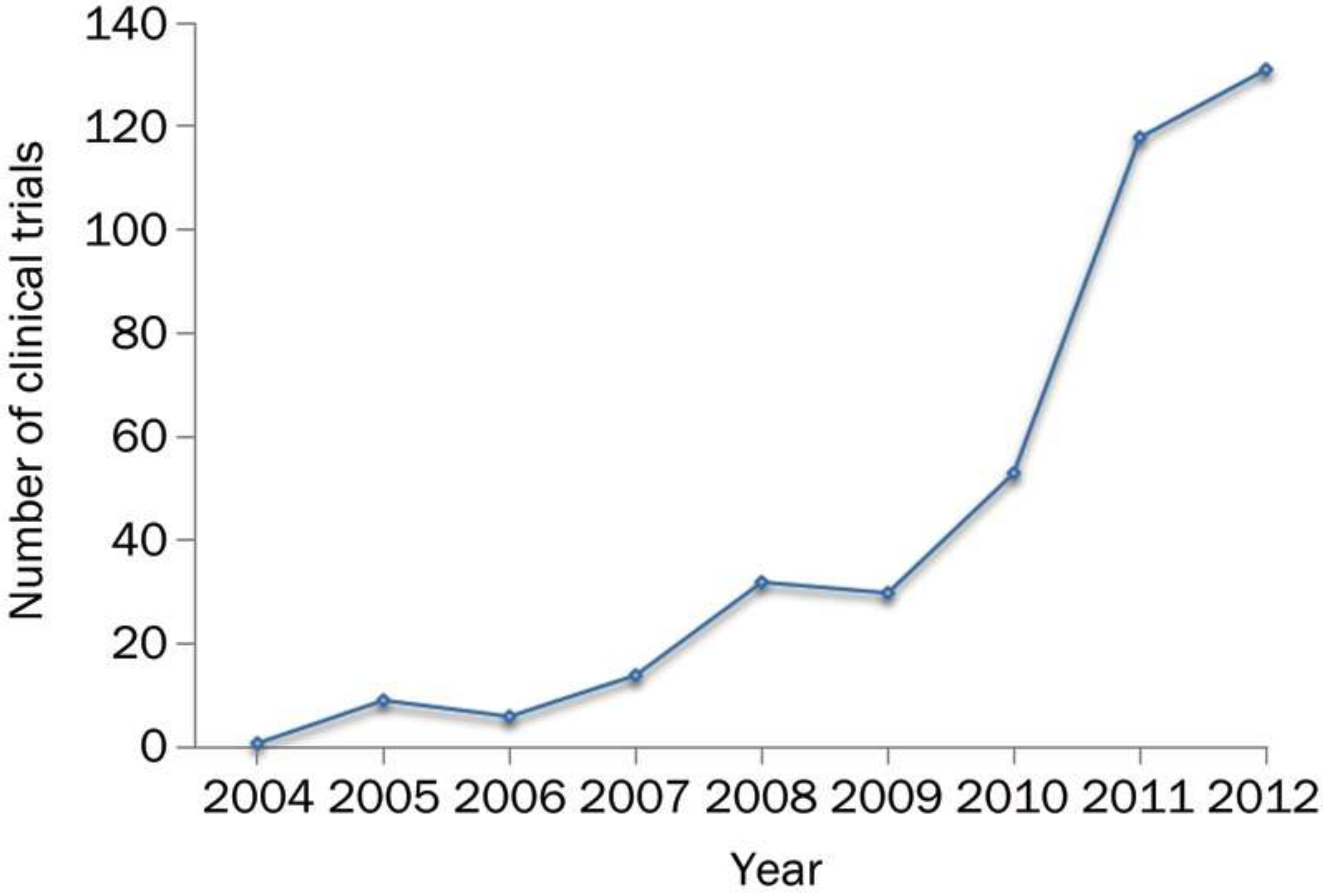




Nombela-Arrieta et al., Nat Rev Mol Cell Biol, 2011;12(2): 126-31.

Stem Cell Research

Number of registered clinical trials of MSCs



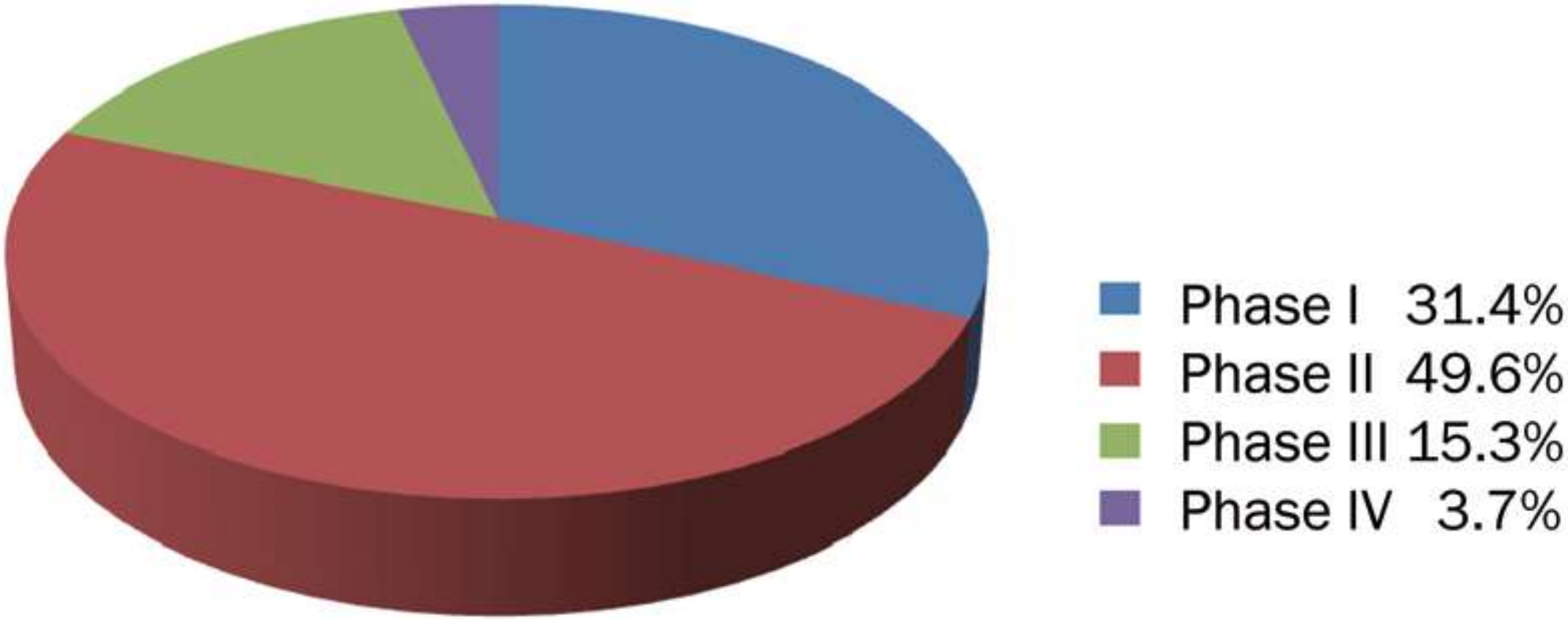
Wei et al., Acta Pharmacologica Sinica, 2013;34: 747–754

In vivo animal models of MSC infusion for tissue repair

Context	*Outcome*
Mouse, EAE	Prevention of EAE development
Mouse, SLE	Ameliorated signs and symptoms of SLE
Mouse, STZ diabetes	Ameliorated diabetes and kidney disease
Rat, glomerulonephritis	Stimulated glomerular healing
Mouse, AKI	Ameliorated renal function and tubular cell injury
Spinal cord injury, stroke	Displayed protection of neurons from damage
Rat, experimental colitis	Stimulated intestinal mucosa healing
Mouse, endotoxin-induced acute lung injury	Improved animal survival
Rat, acute hepatic failure	Protected against hepatic injury
Mouse, rat, pig, myocardial infarction	Improved cardiac function
Mouse, CIA	No beneficial effect; accentuation of Th1 response

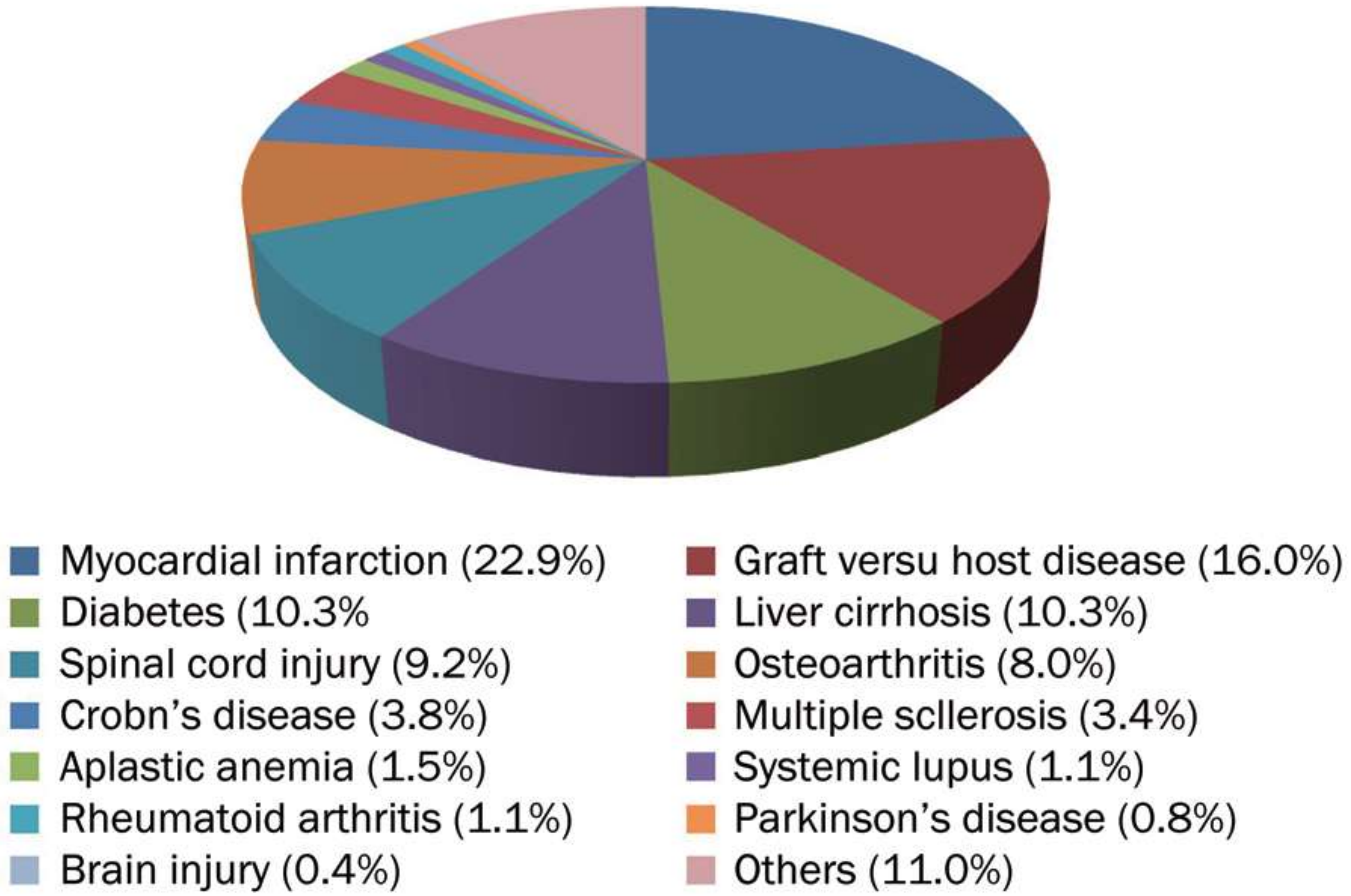
Bernardo et al., Bone Marrow Transplantation, 2012;47: 164–171

Clinical phases of MSCs-based therapy



Wei et al., Acta Pharmacologica Sinica, 2013;34: 747–754

Common diseases now treated with MSCs



Wei et al., Acta Pharmacologica Sinica, 2013;34: 747–754

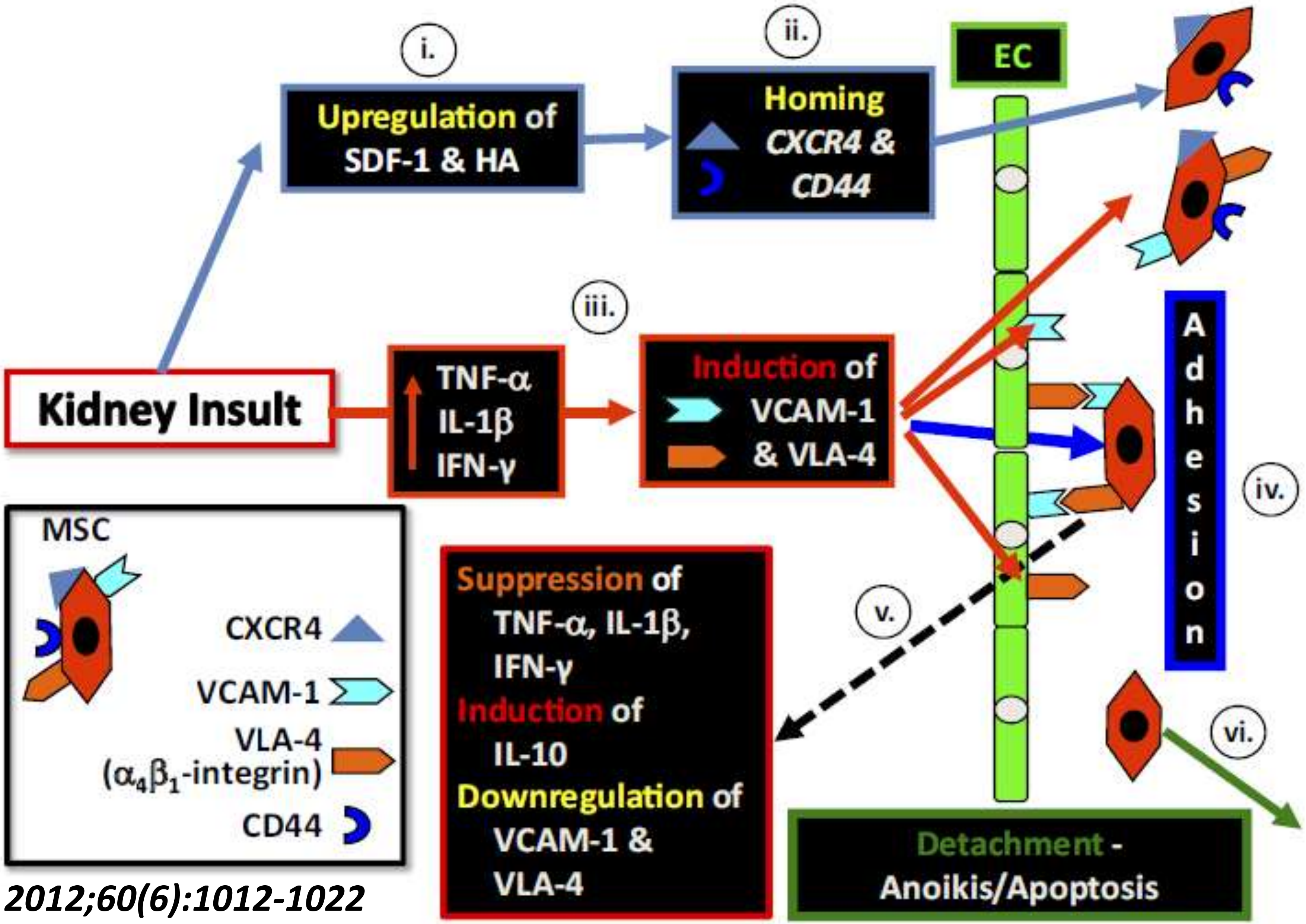
Future uses of MSCs in Regenerative Medicine

Context	*Possible mechanisms*
Diabetes	Increased insulin production; repair of renal glomeruli
Refractory SLE	Immunomodulatory and anti-inflammatory effect
Acute renal damage (AKI)	Stimulate glomeral/tubular healing, inhibit oxidative damage
Kidney transplantation	Immunomodulatory effect, prevent graft rejection
Acute lung injury	Anti-inflammatory and anti-fibrotic effect
Wound healing (diabetic foot, severe limb ischemia, radiation injury)	Anti-inflammatory effect, stimulate functional recovery

Bernardo et al., Bone Marrow Transplantation, 2012;47: 164–171

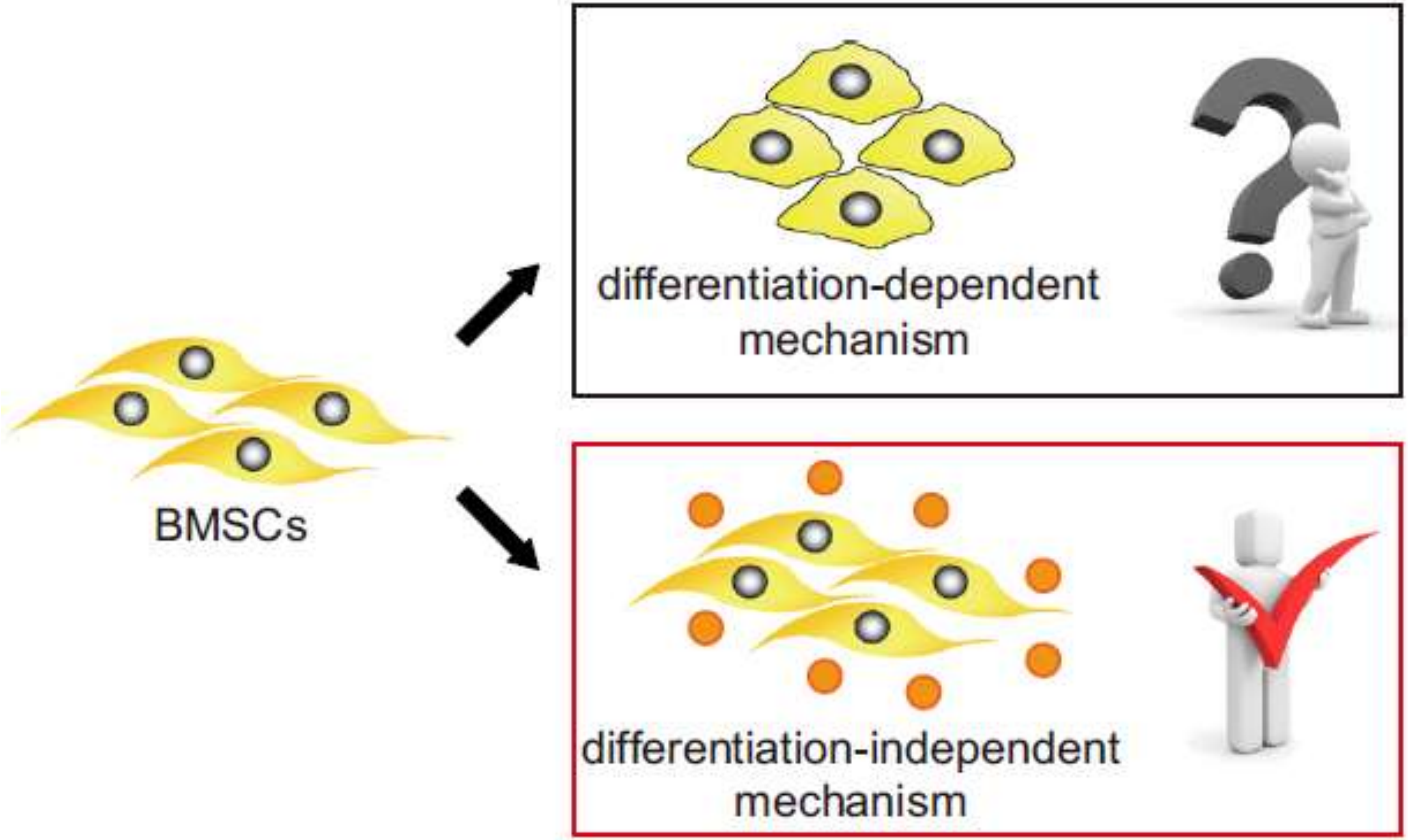
Pathophysiological role in renal repair

I. Homing

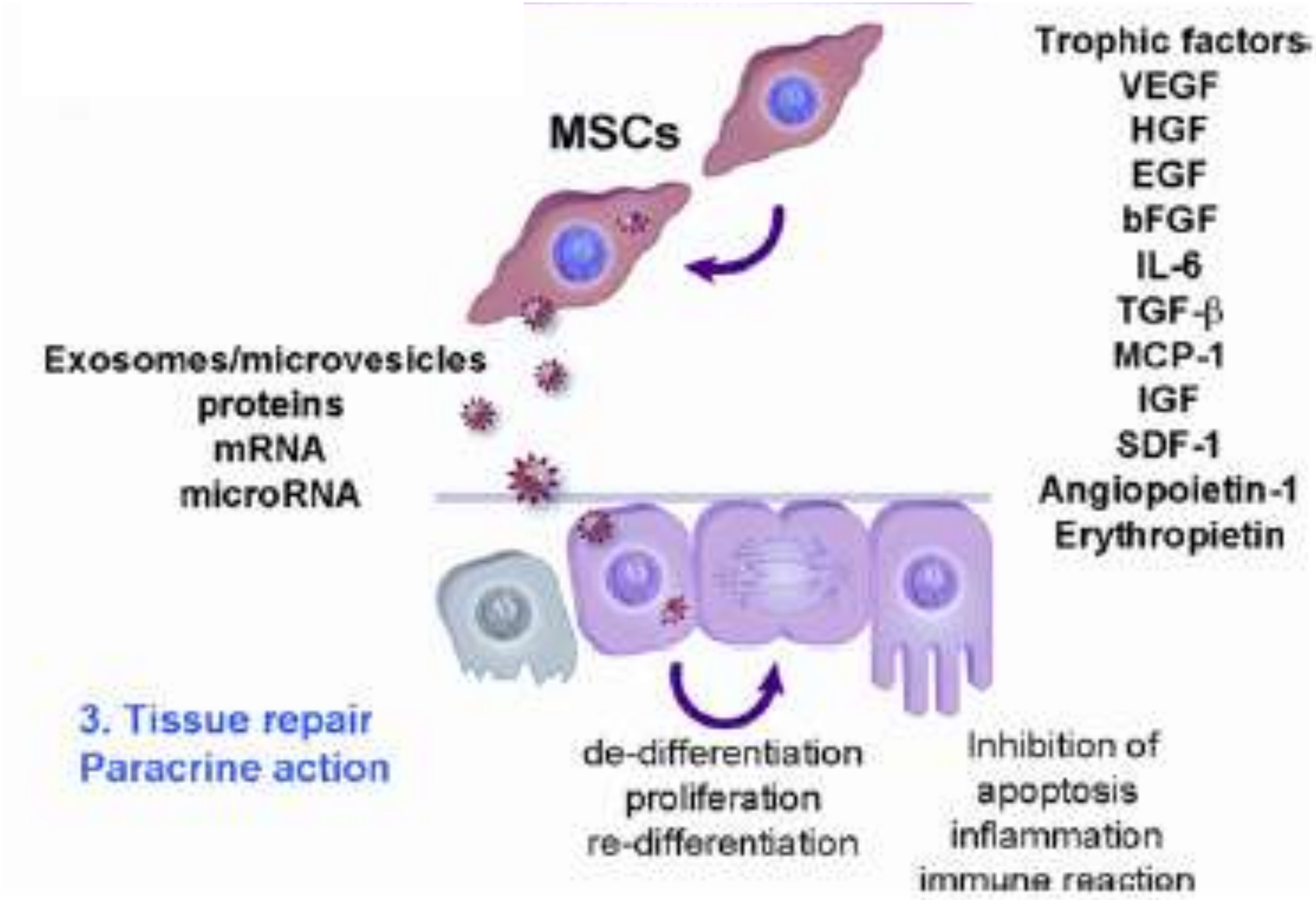


Tögel et al., Am J Kidney Dis. 2012;60(6):1012-1022

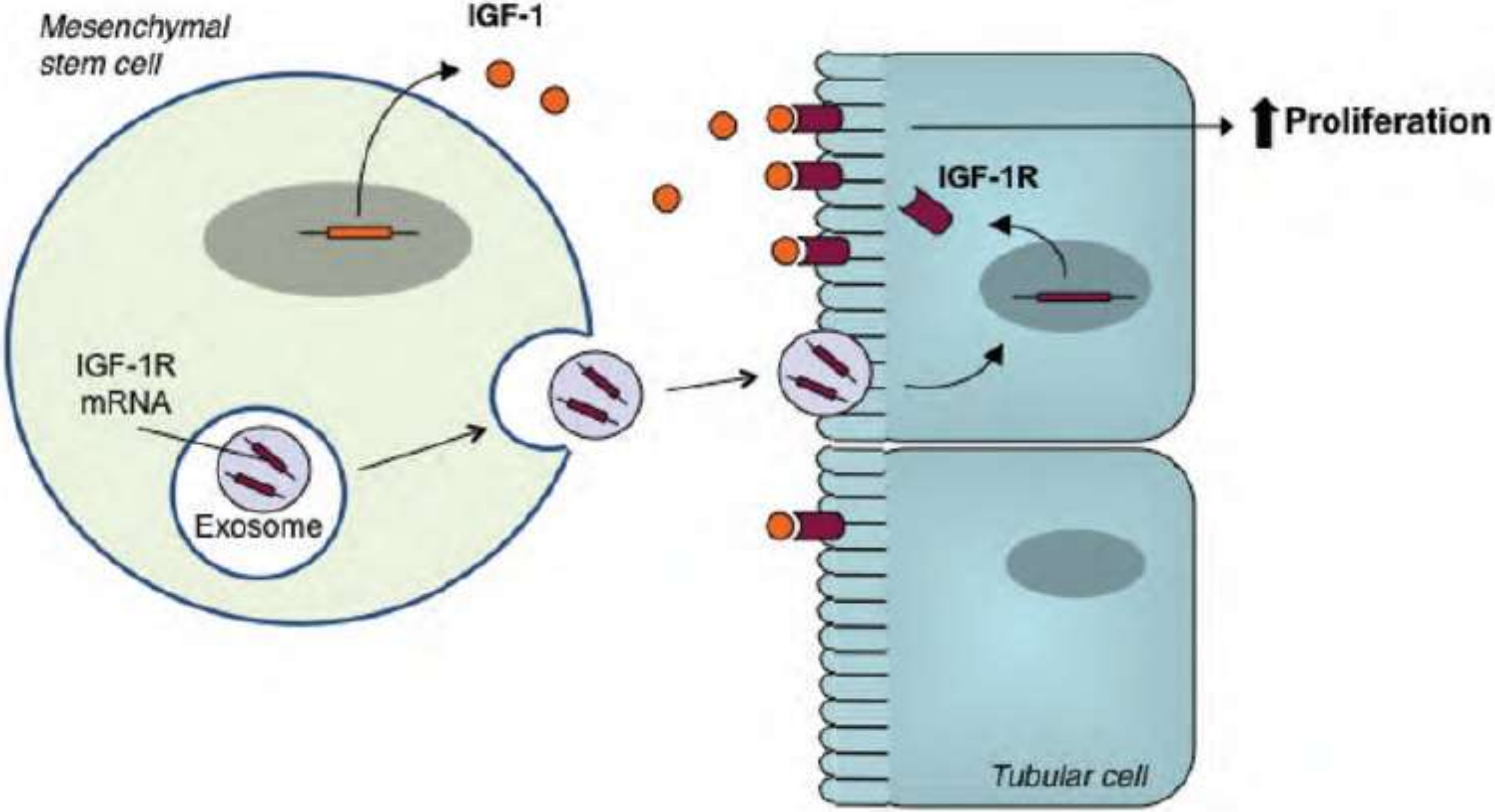
II. Repair



Liu et al., Life Sciences, 2014;115: 1–7

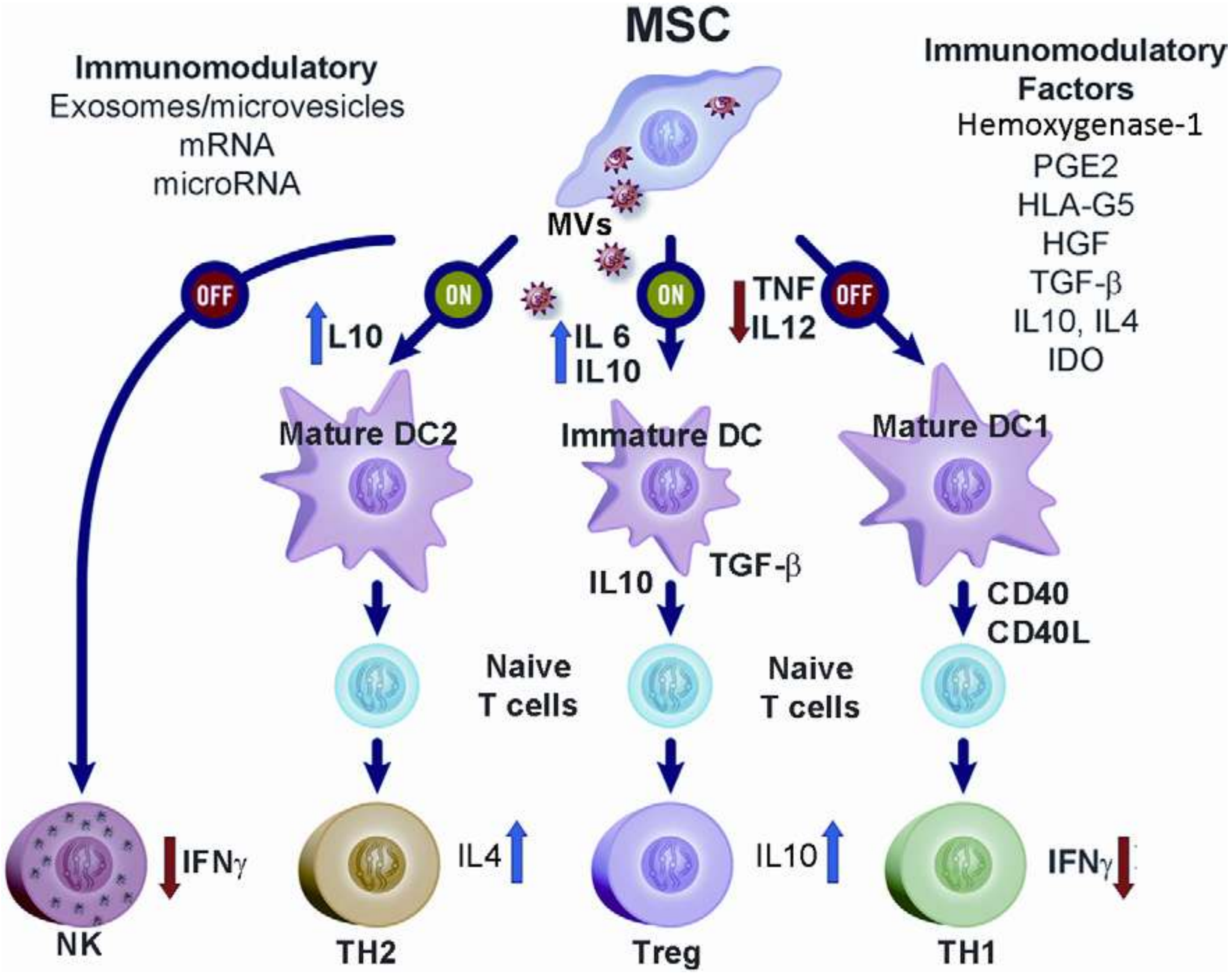


Cantaluppi et al., Am J Kidney Dis. 2013;61(2):300-309

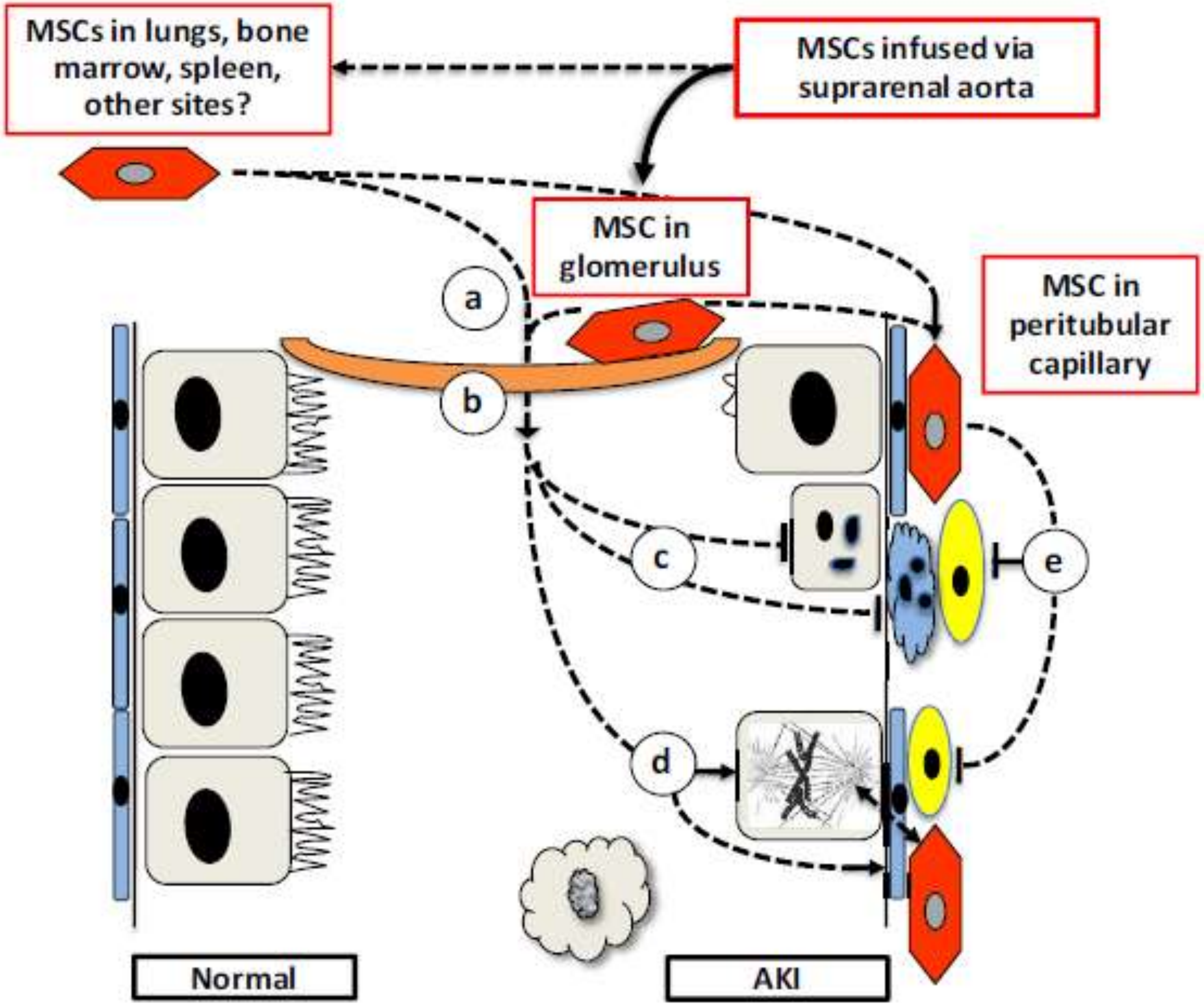


Morigi et al., Nephrol Dial Transplant, 2013;28: 788–793

Immunomodulatory



Cantaluppi et al., Am J Kidney Dis. 2013;61(2):300-309



Tögel et al., Am J Kidney Dis. 2012;60(6):1012-1022

MSCs therapy in AKI

I. Animal Models

NEPHROLOGY

Nephrology **18** (2013) 201–208

Original Article

Systematic review and meta-analysis of mesenchymal stem/stromal cells therapy for impaired renal function in small animal models

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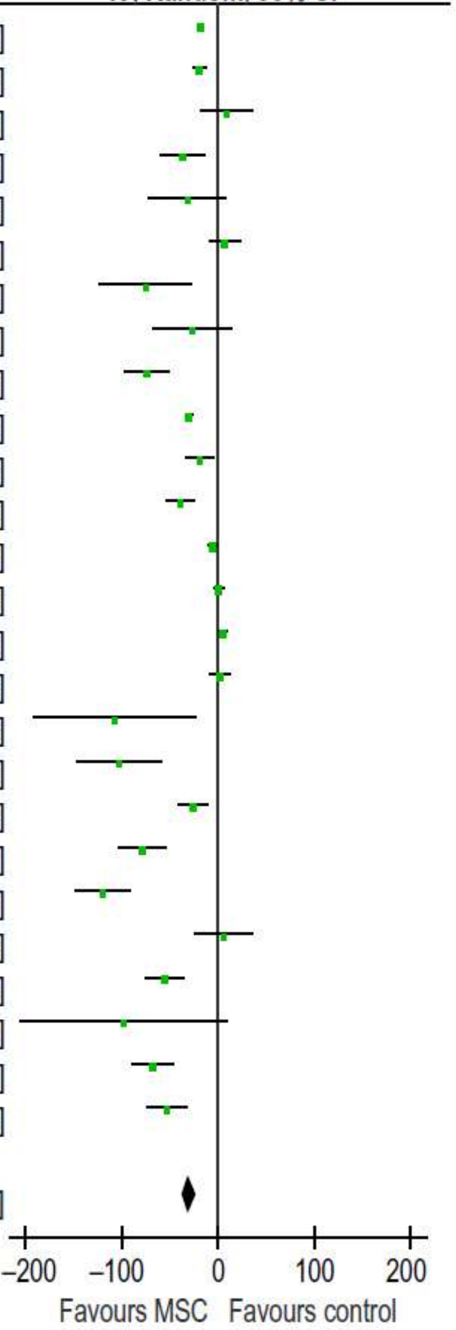
Different influencing factors of MSC therapy

Author (year)	n	Type of animal	Type of injury	MSC type	Number of MSC	Route of delivery	Time of MSC therapy after injury	Time point of Scr measurement
Bi *et al*. (2007)[5]	10	Mice	Toxic	rMSC	0.2×10^6	Intravenous	2 days	3 days
Bruno *et al*. (2009)[6]	16	Mice	Toxic	rMSC	7.5×10^4	Intravenous	3 days	5 days
Burst *et al*. (2009)[7]	28	Rat	IRI	rMSC	2×10^6	Intravenous/ Intra-renal	1 h	1 day
Caldas *et al*. (2009)[8]	10	Rat	Chronic	rMSC	1.5×10^6	Intra-renal	<1 day	120 days
Costa *et al*. (2009)[9]	14	Rat	Chronic	rMSC	0.2×10^6	Intravenous	14 days	84 days
Duffield *et al*. (2005)[10]	14	Mice	IRI	rMSC	0.5×10^6	Intra-renal	2 h	1 day
Eliopoulos *et al*. (2010)[11]	10	Mice	Toxic	rMSC	5×10^6	Intraperitoneal	2 days	4 days
Herrera *et al*. (2004)[12]	24	Mice	Toxic-ischemic	rMSC	1×10^6	Intravenous	3 days	5 days
Kirpatovskii *et al*. (2006)[19]	11	Rat	Chronic	Human foetal MSC	1×10^6	Intra-renal	<1 h	20–21 days
Kunter *et al*. (2006)[14]	15	Rat	Antibodies	rMSC	2×10^6	Renal artery	2 days	6 days
Kunter *et al*. (2007)[15]	19	Rat	Antibodies	rMSC	2×10^6	Intra-arterially	2 days	8 days
Lee *et al*. (2010)[16]	32	Rat	Chronic	rMSC	3×10^6	INTRAVENOUS	1 day, 8 days, 15 days, 22 days, 29 days	35 days
Magnasco *et al*. (2008)[17]	22	Rat	Toxic	rMSC	0.5×10^6 3×10^6 9×10^6	Intravenous/ intra-aortal/ Intraperitoneal	<1 h	49 days
Manna *et al*. (2011)[18]	12	Rat	IRI	FMhMSC	1×10^6	Intra-renal	<1 h	1 day
Martino *et al*. (2010)[19]	10	Rat	Cellular Rejection	rMSC	3×10^6	Renal artery	<1 h	3 days
Nemeth *et al*. (2009)[20]	27	Mice	Sepsis	hMSC	1×10^6	Intravenous	<1 h	4 days
Qian *et al*. (2008)[21]	6	Rat	Toxic-ischemic	hMSC	1×10^4	Intravenous	2–3 days	5 days
Sun *et al*. (2008)[22]	40	Rat	Toxic-ischemic	rMSC	2×10^6	Intra-aortal	2 days	2 days
Togel *et al*. (2005)[23]	12	Rat	IRI	rMSC	1×10^6	Carotid artery	<1 h	2 days
Togel *et al*. (2009)[24]	36	Rat	IRI	rMSC	0.5×10^6 2×10^6 5×10^6	Carotid artery	<1 h	1 day
Villanueva *et al*. (2011)[25]	14	Rat	Chronic	rMSC	0.5×10^6	Intravenous	<1 h	35 days

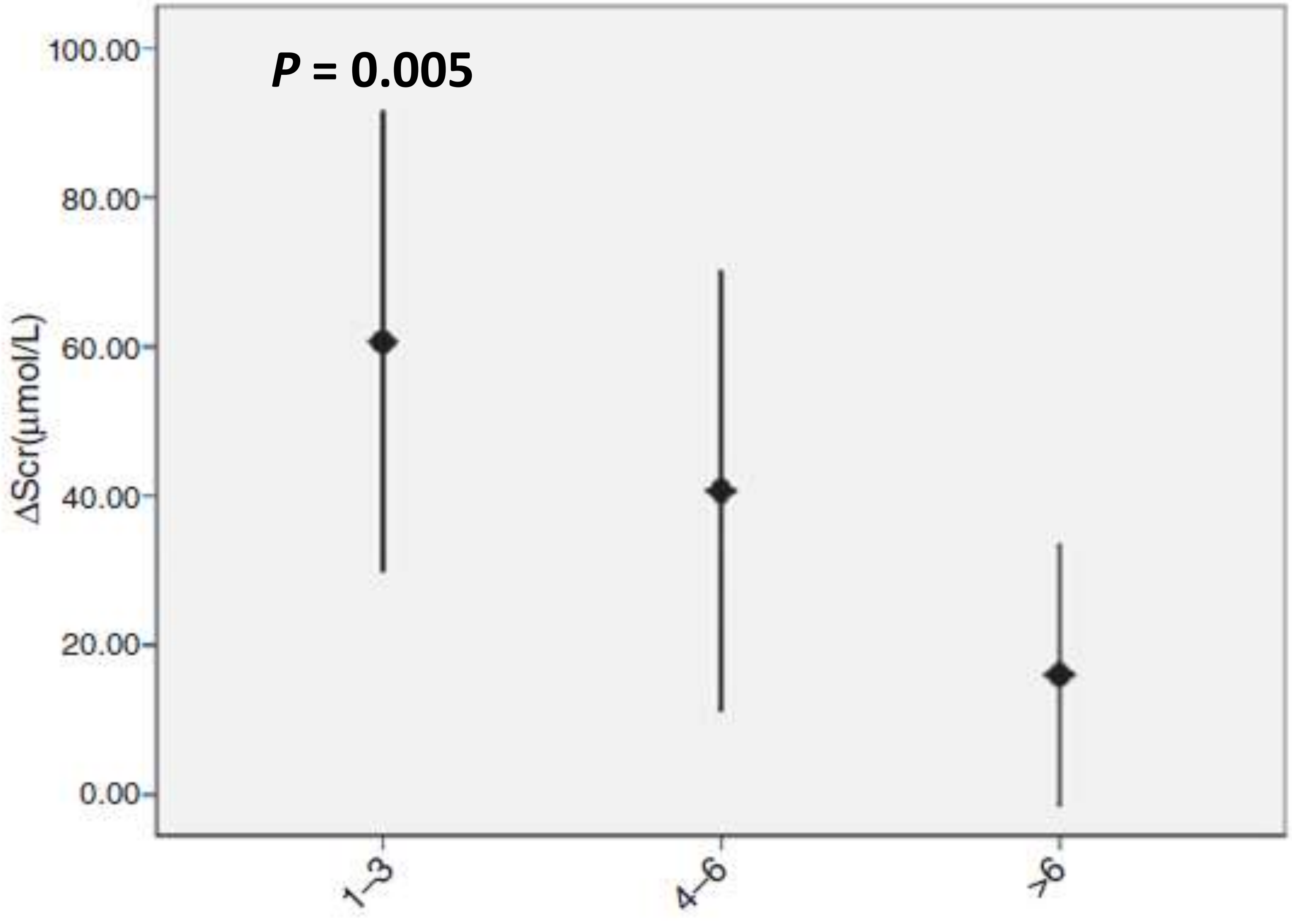
	MSC			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bi 2007	9.72	0.88	5	27.4	0.88	5	5.9%	–17.68 [–18.77, –16.59]	
Bruno 2009	29.12	5.3	8	48.62	7.07	8	5.7%	–19.50 [–25.62, –13.38]	
Burst 1 2009	113.15	28.29	7	104.31	22.98	7	3.2%	8.84 [–18.16, 35.84]	
Burst 2 2009	67.18	18.56	7	104.31	22.98	7	3.8%	–37.13 [–59.01, –15.25]	
Caldas 2009	83.98	8.84	5	115.8	44.2	5	2.1%	–31.82 [–71.33, 7.69]	
Costa 2009	106	17.68	7	99	10.6	7	4.7%	7.00 [–8.27, 22.27]	
Duffield 2005	84.86	25.64	7	160	58.34	7	1.6%	–75.14 [–122.35, –27.93]	
Eliopoulo 2010	67	22	5	94	40	5	2.0%	–27.00 [–67.01, 13.01]	
Herrera 2004	25	8	12	99	38	12	3.8%	–74.00 [–95.97, –52.03]	
Kirpatovskii 2006	56	2	6	86	3	5	5.9%	–30.00 [–33.08, –26.92]	
Kunter 2006	57	19	9	76	9	6	4.8%	–19.00 [–33.35, –4.65]	
Kunter 2007	86	15	10	125	16	9	4.8%	–39.00 [–52.99, –25.01]	
Lee 2010	43.32	6.19	16	48.62	5.3	16	5.8%	–5.30 [–9.29, –1.31]	
Magnasco 1 2008	28.29	4.42	4	27.4	1.77	5	5.8%	0.89 [–3.71, 5.49]	
Magnasco 2 2008	32.71	2.65	3	27.4	1.77	3	5.9%	5.31 [1.70, 8.92]	
Magnasco 3 2008	29.17	7.07	2	27.4	1.77	5	5.3%	1.77 [–8.15, 11.69]	
Manna 2011	170.61	31.82	6	277.58	99.9	6	0.6%	–106.97 [–190.86, –23.08]	
Martino 2010	115.8	33.6	5	218.35	37.13	5	1.8%	–102.55 [–146.44, –58.66]	
Nemeth 2009	28.29	9.72	14	53.92	25.64	13	4.7%	–25.63 [–40.47, –10.79]	
Qian 2008	82	9	3	161	19	3	3.5%	–79.00 [–102.79, –55.21]	
Sun 2008	211	38	20	331	52	20	3.0%	–120.00 [–148.23, –91.77]	
Togel 1 2009	184.76	31.82	6	179.45	18.56	6	2.9%	5.31 [–24.17, 34.79]	
Togel 2 2009	123.76	15.91	6	179.45	18.56	6	4.1%	–55.69 [–75.25, –36.13]	
Togel 2005	192.71	96.36	6	290.84	93.7	6	0.4%	–98.13 [–205.68, 9.42]	
Togel 3 2009	111.38	18.56	6	179.45	18.56	6	3.9%	–68.07 [–89.07, –47.07]	
Villanueva 2011	35.36	8.84	7	88.4	26.52	7	3.9%	–53.04 [–73.75, –32.33]	
Total (95% CI)			192			190	100.0%	–30.03 [–37.09, –22.97]	

Heterogeneity: $Tau^2 = 218.28$; $\chi^2 = 530.67$, df = 25 ($P < 0.00001$); $I^2 = 95\%$

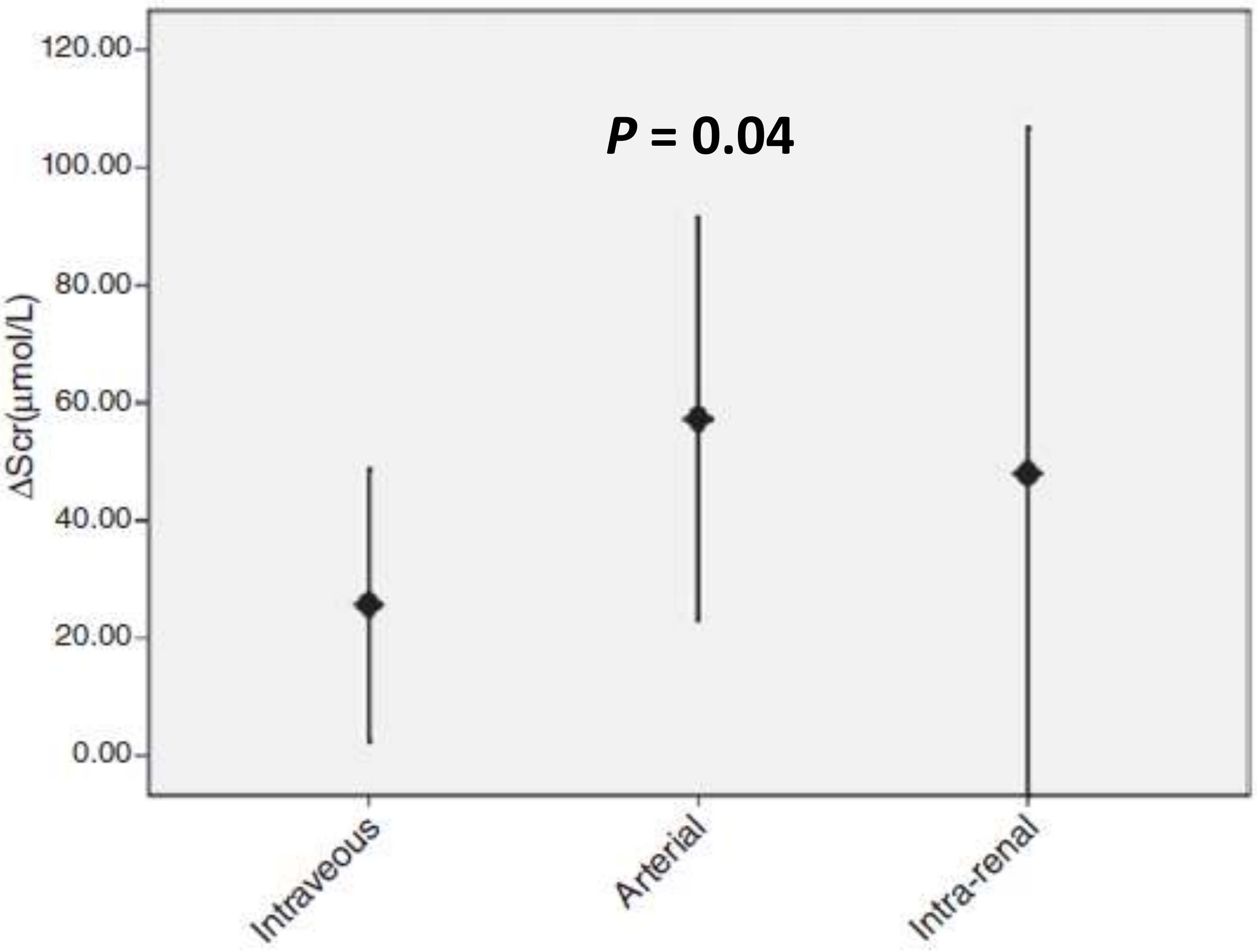
Test for overall effect: $Z = 8.34$ ($P < 0.00001$)



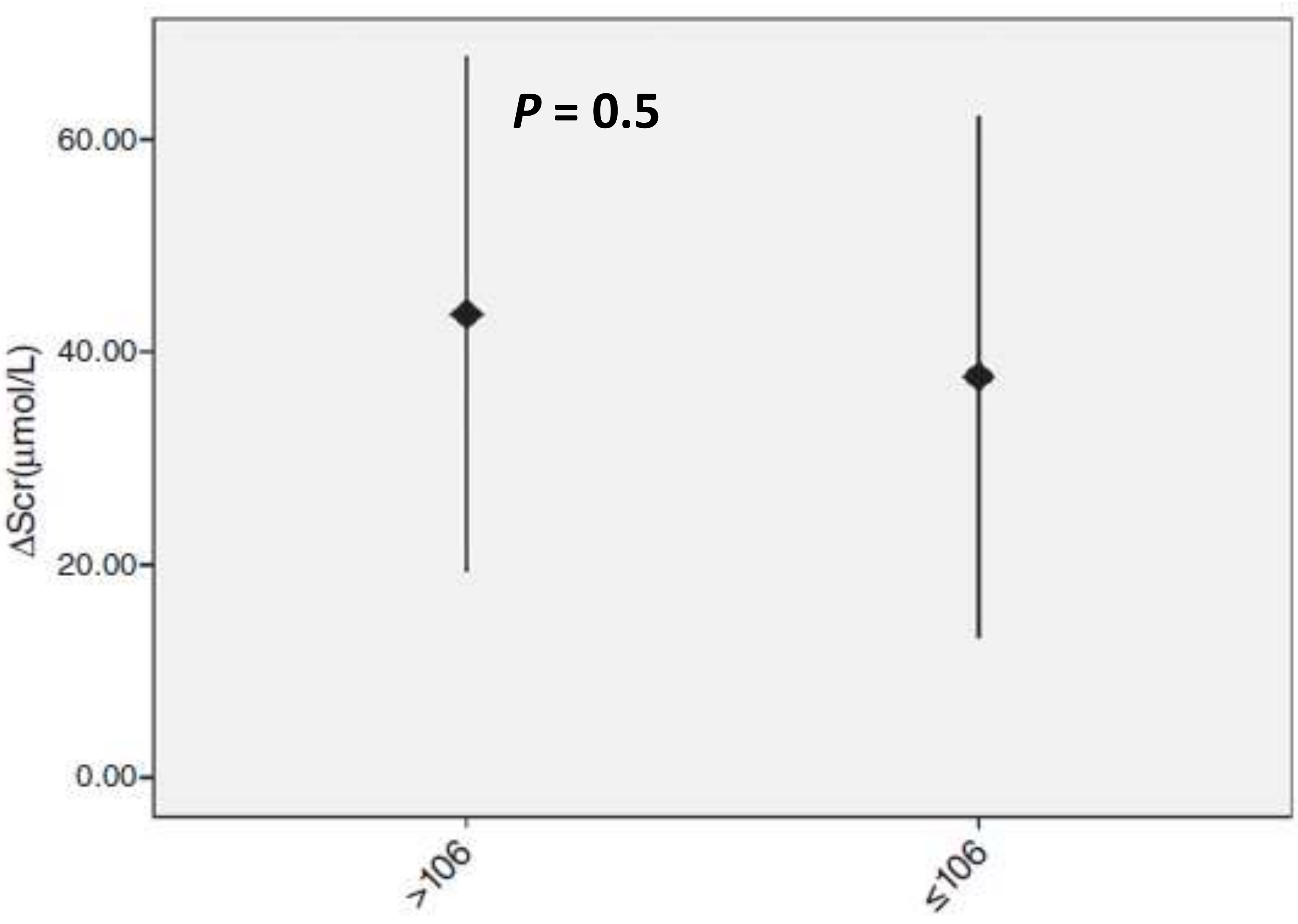
Time point of Scr measurment (Days)



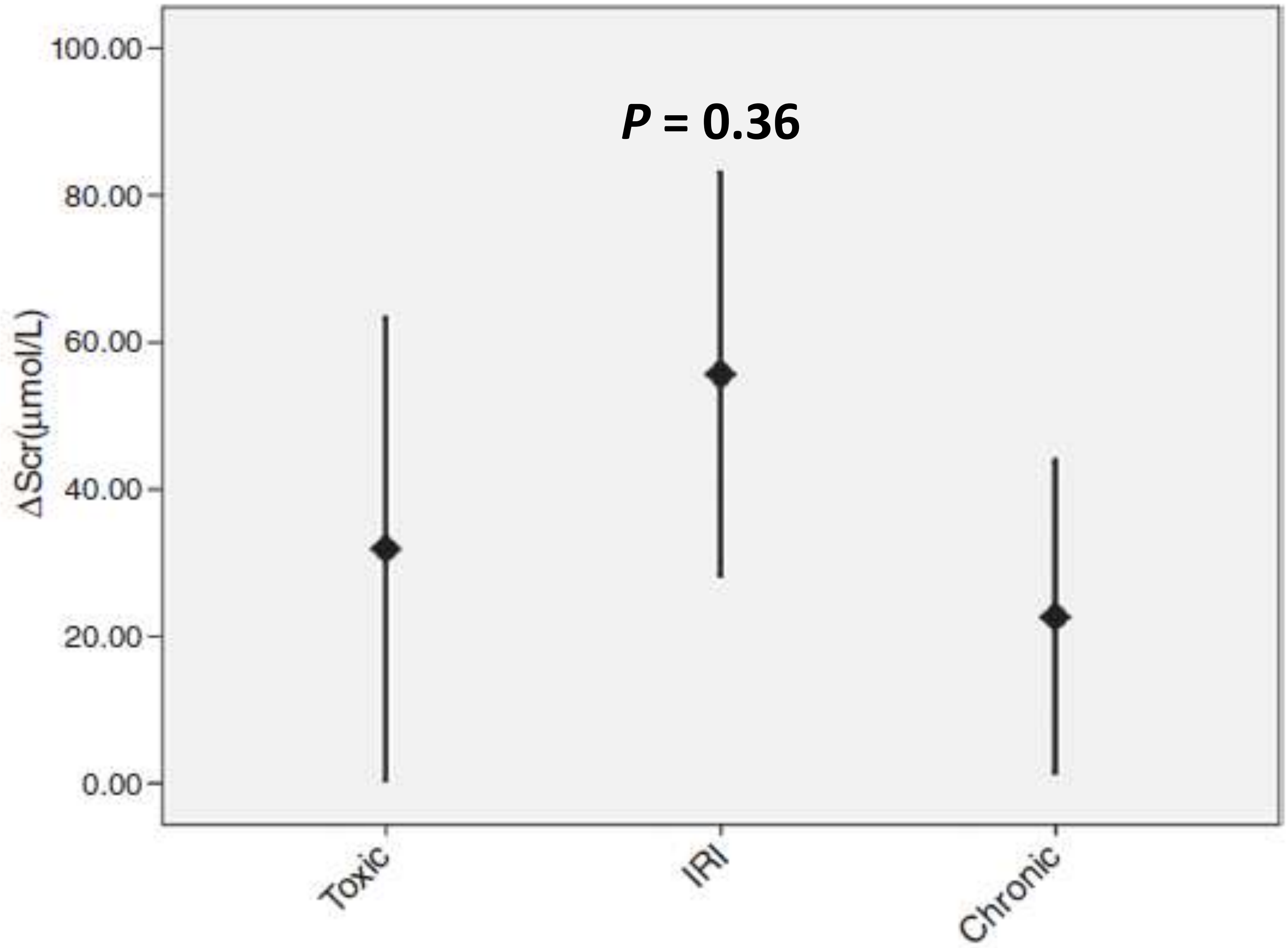
Routes of cell delivery



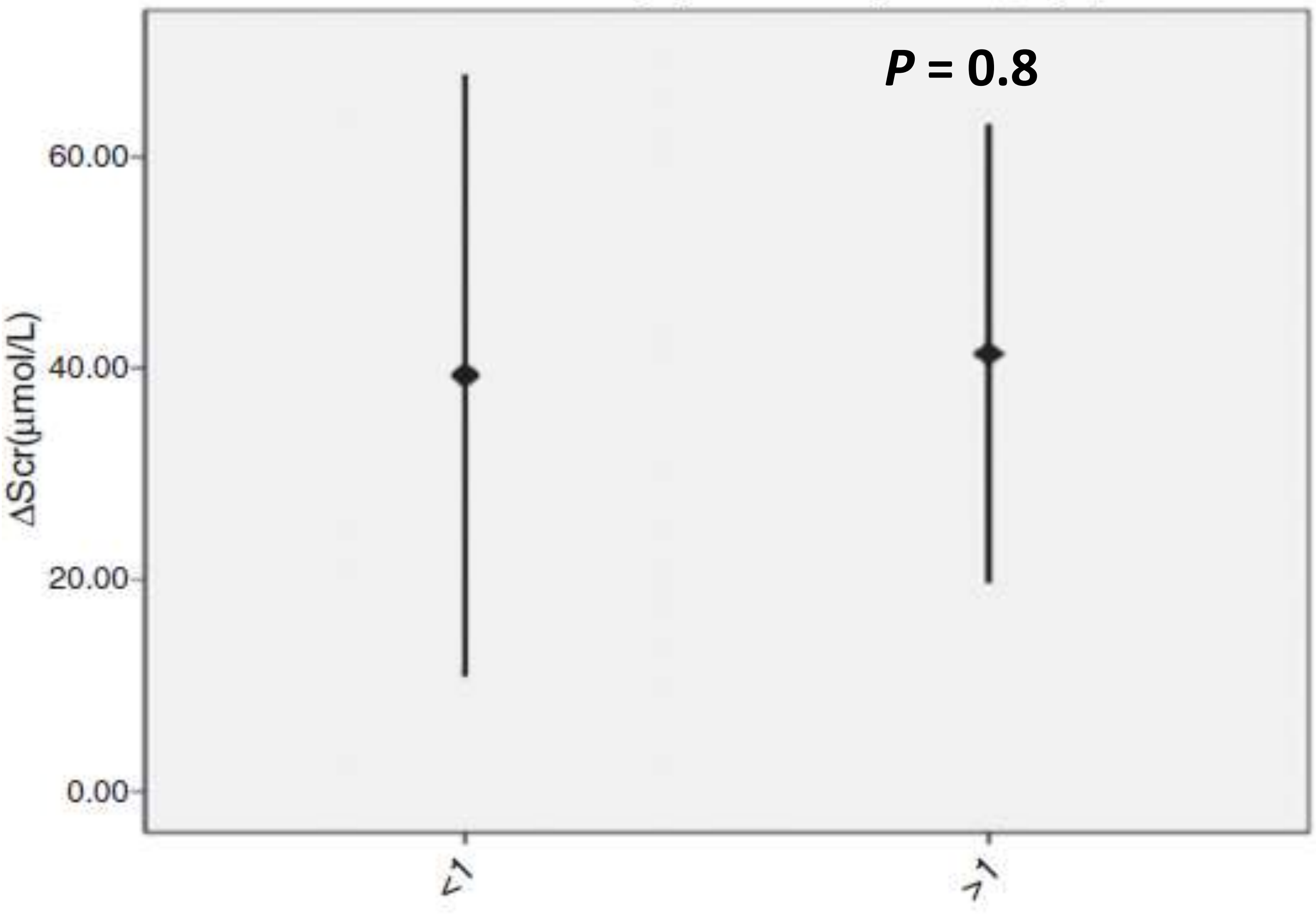
Cell number



Renal failure model



Time between injury and cell injection (Days)



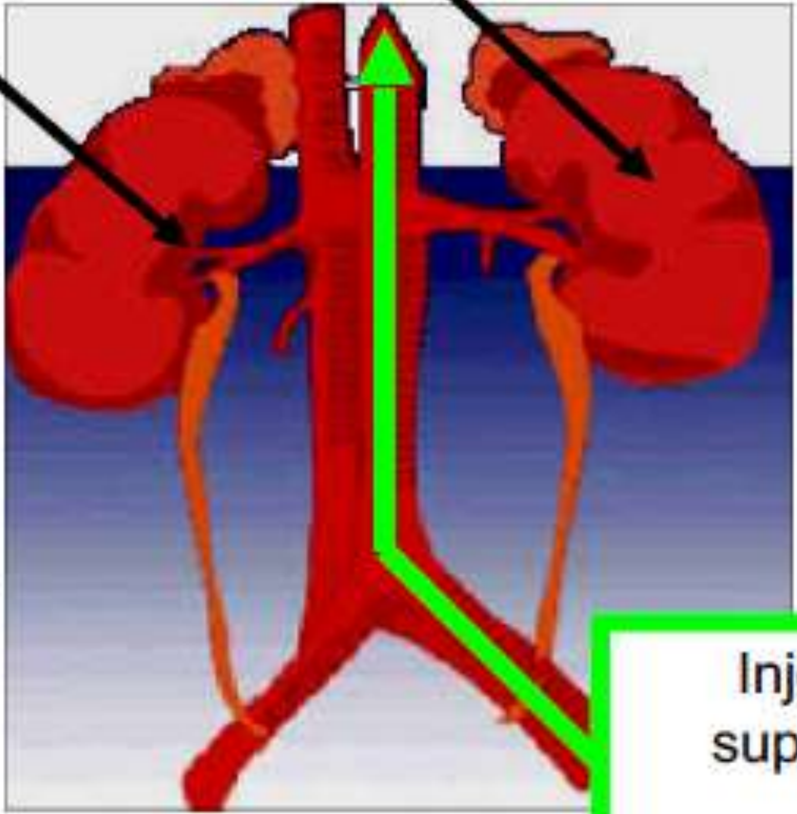
II. Human Clinical Studies

Study	Phase	Aim	Enrolled patients	Status
NCT00733876	Phase 1	To determine the safety of the administration of allogeneic MSCs at defined doses in patients with high risk of developing AKI after undergoing on-pump cardiac surgery	15	Completed[52]
NCT01275612	Phase 1	To test the feasibility and safety of systemic infusion of donor *ex-vivo* expanded MSCs to repair kidney and improve function in patients with solid organ cancers who develop acute renal failure after chemotherapy with cisplatin	3 (estimated enrollment 9 patients)	Ongoing and recruiting patients
NCT01602328	Phase 2	To evaluate kidney recovery after a single injection of allogeneic bone marrow derived MSCs in patients who experience kidney injury within 48 h of their cardiac surgery	156	Terminated

Bianchi et al., World J Stem Cells 2014;26; 6(5): 644-650

Kidney "Insult":
on-pump cardiac surgery

15-20% of high-risk patients develop AKI (by *RIFLE, AKIN)*



Dose Escalation: 3 groups of 5 patients each received a pre-determined dose of ***allogeneic*** **MSC**

Follow-up:
Close: 6 months
Total: 3 years

Inject ***allogeneic*** **MSC** into suprarenal aorta after patient comes off pump

Tögel et al., Am J Kidney Dis. 2012;60(6):1012-1022

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Conclusion

- AKI is an increasingly common medical problems with no proven effective strategy to enhance renal repair.
- MSCs is a promising regenerative and immunomodulatory type of cell-based therapy
- MSCs yielded an excellent therapeutic effect in animal models of AKI
- We need many clinical studies for the therapeutic effect of MSCs in AKI before adopting this therapeutic tool in human

THANK YOU